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Disclosures

- CSL Behring: Speaker, Research, Advisory Panel
- BioCryst: Advisory
- Dyax: Speaker, Research, Advisory Panel
- Pharming: Research
- Shire HGT: Speaker, Research, Advisory Panel
- ViroPharma: Speaker, Research, Advisory Panel

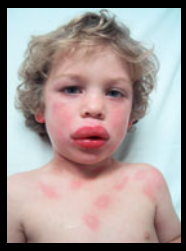
Learning Objectives

Session participants should be able to:

1) Discuss the differential diagnosis for urticaria and angioedema and properly assess patients with these conditions
2) Identify patients with physical urticaria/angioedema
3) Summarize current and emerging therapies for urticaria and angioedema
4) Describe an evidence-based and cost-effective approach to diagnosis and management of patients with chronic urticaria/angioedema

Angioedema

- Described by Donati in 1586, Milton in 1876 and Quincke in 1882
- Well-demarcated non-pitting edema
- Often caused by same pathological factors that cause urticaria
- Reaction occurs deeper in dermis and subcutaneous tissues
- Face, tongue, lips, eyelids most commonly affected
- May be life-threatening due to airway swelling and asphyxia



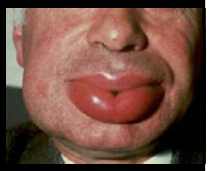
Case 1 - John

- John is a 34 year-old male
- Develops mild oral pruritus and tingling during lunch of chicken salad
- Progression to include cutaneous pruritus with urticaria while driving back to office
- Stopped at ED en route and presents with swollen lips and tongue that developed over past 45 minutes
- Now c/o abdominal pain and nausea
- Began lisinopril 5 days ago for hypertension
- Has history of tree nut induced anaphylaxis

Case courtesy of Marc Riedl

Case 1 - John

- While waiting in triage, develops severe diffuse pruritus and progressive lip swelling
- To ED bed with oropharyngeal and tongue angioedema, drooling, facial erythema, periorbital edema
- On auscultation, abnormal upper and lower airway exam: expiratory stridor and wheezing



Case 1 - John

- Administered epinephrine and antihistamines with symptom improvement in 15 minutes
- Cutaneous symptoms recur 40 minutes later
- Clinical response to re-dosing of epinephrine
- Patient discharged 3 hours later in improved condition

Case 1 - Considerations

- Etiology
  - Allergic – tree nut allergy
  - ACE Inhibitor - induced
  - Idiopathic
  - HAE with or without C1 INH deficiency
- History
  - Progression of attack
  - Associated symptoms such as pruritus and urticaria
- Response to therapy
  - Antihistamine, corticosteroid, epinephrine responsive or not

Causes of Angioedema

- Allergic: Foods, drugs, insect stings/bites
- Radiocontrast media
- ASA and other NSAID'S
- Autoimmune
- ACE inhibitor-induced
- Idiopathic
  - Histamine-induced/Mast cell mediated
  - Bradykinin-induced
- C1 inhibitor deficiency
  - Hereditary – Types I, II
  - Acquired
- Hereditary with normal C1 Inhibitor

Agostoni A, *J Allergy Clin Immunol*. 2004;114:S51-S131.
Cichon S, *Am J Hum Genet*. 2006;79:1098-1104.

Classification of Recurrent Angioedema without Urticaria

Pattern	Name	Subtype	Comment
Familial			
	HAE due to C1INH deficiency	Type I	Caused by mutation of SERPING 1 leading to functional C1INH deficiency; Bradykinin mediated
		Type II	Caused by mutation of SERPING 1 leading to functional C1INH deficiency; bradykinin mediated
	HAE with normal C1INH	f XII mutation	Associated with mutations of f XII likely bradykinin-mediated
		Unknown cause	Genetic mutation unknown likely bradykinin-mediated
Sporadic			
	Acquired C1INH deficiency		Associated with underlying malignancy or disease or anti-C1INH autoantibody resulting in increased catabolism of C1INH; bradykinin-mediated
	ACE–Inhibitor related		Decreased catabolism of bradykinin likely bradykinin-mediated
	Allergic		Mast cell degranulation involving specific IgE
	Unknown etiology	Histaminergic	Mast cell degranulation
		Nonhistaminergic	Possibly bradykinin-mediated

Zuraw BL et al. 2012 in press

Causes of Angioedema Without Urticaria

Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, *n* = 776

	Patients		M:F ratio	Age at onset, yr	
	No.	%		Median	Range
Related to a specific factor*	124	16	0.51	39	13-76
Autoimmune disease/infection	55	7	0.62	49	3-78
ACE inhibitor-related	85	11	0.93	61	32-84
C1-inhibitor deficiency	197	25			
Hereditary	183		0.88	8	1-34
Acquired	14		1.8	56.5	42-76
Unknown (idiopathic) etiology	294	38			
Histaminergic	254		0.56	40	7-86
Nonhistaminergic	40		1.35	36	8-75
Peripheral/generalized edema	21	3	0.17	—	

Note: M = male, F = female, ACE = angiotensin-converting enzyme.
*A food, drug, insect bite, environmental allergen or other physical stimulus.

Zingale LC, et al. *CMAJ*. 2006;175:1065-1070.

Allergic Angioedema

Mast Cell/Histamine-mediated[1,2]

- Associated with exposure to allergens
- Usually associated with pruritus or urticaria
- Swelling normally subsides within 24 hours
- Responsive to epinephrine, antihistamines and/or corticosteroids
- Onset at any age

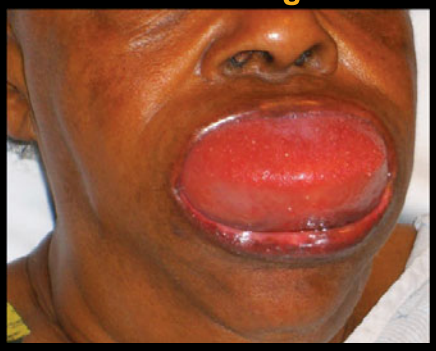
1. Nzeako UC, et al. *Arch Intern Med*. 2001;161:2417-2249.
2. Weldon D. *Immunol Allergy Clin North Am*. 2006;26:603-613.

Angiotensin Converting Enzyme (ACE) – Induced Angioedema

- Now most common exogenous cause of angioedema seen in emergency rooms
- Usually has no concomitant urticaria
- Most likely caused by increased bradykinin levels because bradykinin degradation by ACE is inhibited
- Can cause dramatic swelling of tongue, pharynx, or larynx – may require intubation or tracheostomy

Johnson SP, Jacobsen J, Monster TBM et al. Am. J.Med.118:1428-1429, 2005

ACE – Induced Angioedema



ACE-I Induced Angioedema

- Angioedema develops in 0.1% to 0.5% of those receiving ACE inhibitors. All ACE inhibitors may cause
- Onset can occur from 1st week or longer of use
- Symptoms resolve with cessation of drug, but may persist for days
- Risk factors include obesity, prior endotracheal intubation, face and neck surgery, previous history of angioedema
- Genetic factors may be important
- ACE inhibitors will trigger attacks in those with HAE, so avoid in these patients

Johnson SP, Jacobsen J, Monster TBM et al. Am. J.Med.118:1428-1429, 2005

ACE-I Induced Angioedema

Management

- Management of angioedema depends on site of involvement – securing the airway by intubation may be necessary
- Consider off label use of icatibant or ecallantide to treat swelling
- ALL ACE inhibitors should be avoided
- Angiotensin II receptor blockers (ARB's) should be avoided if alternative therapy effective

Johnson SP, Jacobsen J, Monster TBM et al. Am. J.Med.118:1428-1429, 2005

Idiopathic Angioedema

- Recurrent angioedema, no recognized exogenous precipitating factor. May be associated with urticaria
- Negative testing for antibody to IgE receptor; C1q, C4, C1 inhibitor protein and function norma: Anti-thyroid antibodies elevated in some; perhaps less frequently than in chronic urticaria
- Typically episodes of swelling of lips, cheeks, eyes, tongue, pharynx, extremities, genitalia
- Sub-types:
  - Responsive to antihistamines
  - Non-responsive to antihistamines. Bradykinin likely mediator

Treatment of Acute Episodes of Angioedema

- Epinephrine – if rapidly advancing or laryngeal involvement
- Non-sedating antihistamines (e.g. fexofenadine, desloratadine, cetirizine, loratidine) – up to 4 times the doses used for allergic rhinitis
- Diphenhydramine 50 mg or Hydroxyzine 50-100 mg (for more severe attacks) – repeat in 4-6 hours if need
- Prednisone 40 mg x 1-2 doses and stop
- H2 antihistamines and leukotriene modifiers can be added

Zuberbier T, Asero R, Bindslev-Jensen C. Allergy, 2009; 64: 1427-1443

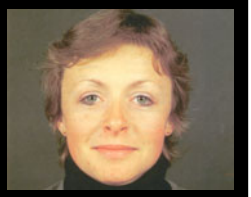
Preventive Therapy of Angioedema

- Avoid known triggers
- A non-sedating antihistamine; possible to use up to 4 times the usual dose for allergic rhinitis
- Add H2-antagonist high dose BID
- May try leukotriene modifier
- If ineffective, diphenhydramine or hydroxyzine at 50 mg QID
- If antihistamines alone are ineffective, try corticosteroids
- Corticosteroid sparing agents such as cyclosporine may be tried but may not be as effective as in urticaria

Zuberbier T, Asero R, Bindslev-Jensen C. Allergy, 2009; 64: 1427-1443

Case 2 - Bonnie

- Bonnie is a 22 year-old female
- Presents to ED with 'scratchy throat' and difficulty swallowing
- URI symptoms over the past 24 hours
- First dose of azithromycin ~18 hours ago
- Awoke this morning with a 'lump in her throat'



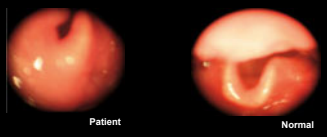
Case courtesy of Marc Riedl

Case 2 - Bonnie

- Over 3 hours in triage/ED develops voice changes
- Difficulty speaking due to raspy voice
- Swallowing uncomfortable
- Reports her breathing is feeling more labored
- Treated with antihistamines and prednisone
- After 30 minutes, reports additional throat tightening
- Given epinephrine
- Symptoms improve for 15-20 minutes
- Symptoms resume progression

Case 2 - Bonnie

- ENT consulted and fiberoptic laryngoscopy confirms moderate epiglottal edema
- Admitted to ICU for observation and management



- After 16 hours, symptoms begin improving
- Patient slowly recovers
- Discharge from hospital after 2 days

Clinical Features of HAE

- Angioedema **without** urticaria
  - Attacks may be preceded by prodromal symptoms (rash, fatigue)
- Angioedema often quite severe
  - Face, oropharynx, GI system, genitourinary tract, extremities
- Attacks prolonged
  - Increasing intensity over 24 hours, resolve in 2–4 days
  - Unresponsive to therapy with antihistamines, corticosteroids, and epinephrine
- Attacks unpredictable with variable severity
- Frequently worsens at puberty, by menses, estrogen-containing drugs, and ACE inhibitors
- Often precipitated by trauma, infection or stress

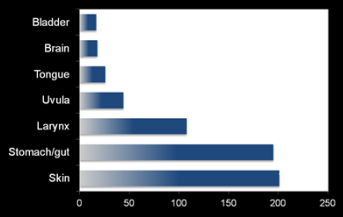
Epidemiology of HAE

- Prevalence difficult to ascertain
  - 75% (+) family history
  - autosomal dominant - 25% spontaneous mutation
  - 280+ mutations of C1-INH gene identified to date
  - estimates of 1 in 30,000 - 1 in 80,000 suggest 4,000 – 10,000 HAE patients in USA
  - no known ethnic or gender differences
- Patients may have frequent and / or severe attacks BUT severity highly variable between patients / within families
- Mortality from laryngeal edema / asphyxiation reported in up to 30% of untreated laryngeal attacks

Frank MM, et al. *Annals Int Med.* 1976;84:580-593.
Agostoni A, et al. *J Allergy Clin Immunol.* 2004;114:S51-S131.
Craig TJ, et al. *Annals Allergy, Asthma, and Immunology.* 2009; 102:366-372.

Location of Symptoms

Number of patients (N=201) experiencing HAE symptoms at various locations

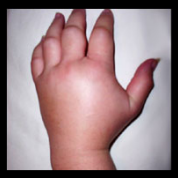


- Most patients have cutaneous and abdominal swelling
- 54% of patients will have laryngeal edema

Bork et al. *Am J Med.* 2006;119(3):267-274;with permission.

HAE Extremity Attacks

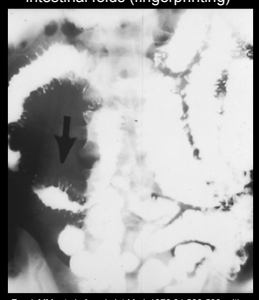
- Affects 96% of patients
- Functionally disabling
  - Hands: difficulty in driving, typing, use of phone
  - Feet: impedes walking, standing
- Interferes with work and school
- Rarely results in hospitalization



Frank MM, et al. *Ann Intern Med.* 1976;82:580-593.
Frank MM. *Immunol Allergy Clin North Am.* 2006;26:653-668.

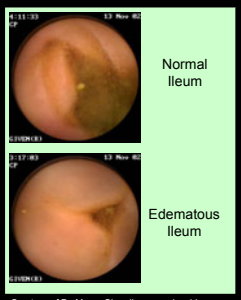
HAE Abdominal Attacks

Spiculation and thickening of intestinal folds (fingerprinting)



Frank MM, et al. *Annals Int Med.* 1976;84:580-593; with permission.

Bowel edema



Courtesy of Dr. Marco Cicardi, personal archive.

HAE Laryngeal Attacks

- Occur in ~ 50% of patients
- Require airway management
- Survey of 58 HAE patients
  - 40% incidence of asphyxiation in untreated laryngeal attacks

Photo courtesy of Frank

Bork K, et al. *Arch Intern Med.* 2003;163:1229-1235.
Bork K, et al. *Mayo Clin Proc.* 2000;75:349-354.

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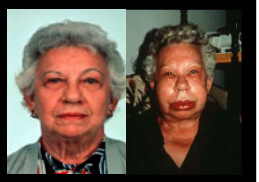

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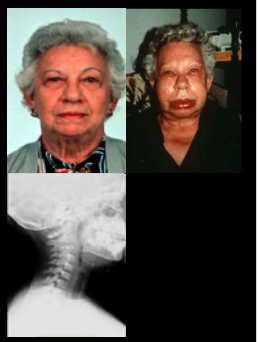

Photos courtesy of Lumry, ACAAI 2011

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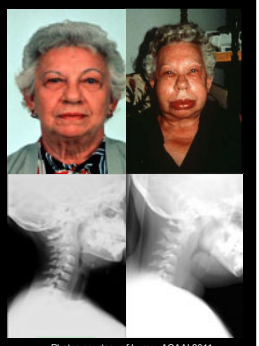

Bork K, et al. *Arch Intern Med.* 2003;163:1229-1235.
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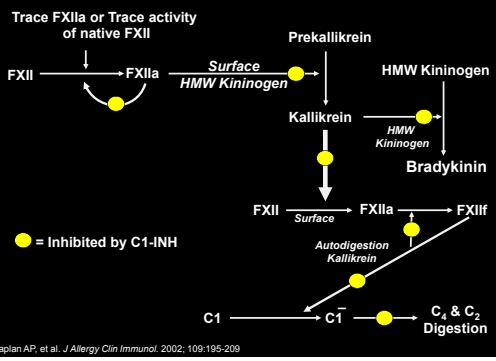
Function of C1-INH



Kaplan AP, et al. *J Allergy Clin Immunol.* 2002; 109:195-209

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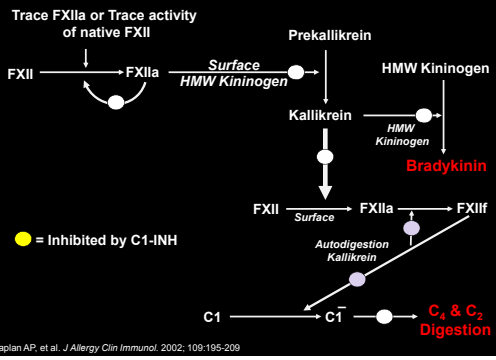

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Complement Profile in Recurrent Angioedema

Type	C1-INH Level	C1-INH Function	C4 Level	C3 Level	C1q Level
HAE type I	<30%	<30%	Low	Normal	Normal
HAE type II	Normal	<30%	Low	Normal	Normal
HAE with normal C1INH	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	<30%	Normal/ Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

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HAE type I	<30%	<30%	**Low**	Normal	Normal
HAE type II	Normal	<30%	**Low**	Normal	Normal
HAE type III	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	**<30%**	Normal/ Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

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HAE type II	Normal	<30%	Low	Normal	Normal
HAE type III	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	**Low**	Low	<30%	Normal/ Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

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HAE type III	Normal	Normal	Normal	Normal	Normal
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ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

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Acquired C1-INH I/II	Low	Low	<30%	Normal/ Low	**Low**
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
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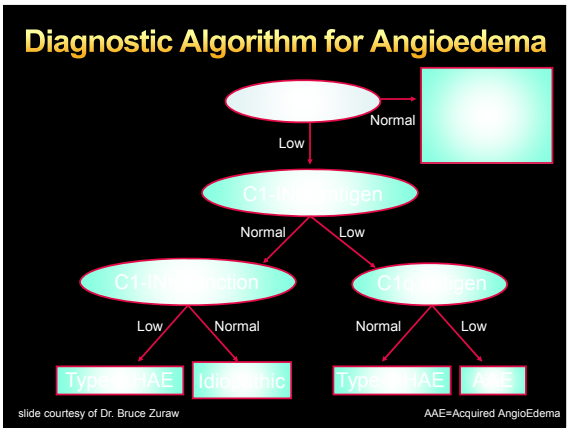
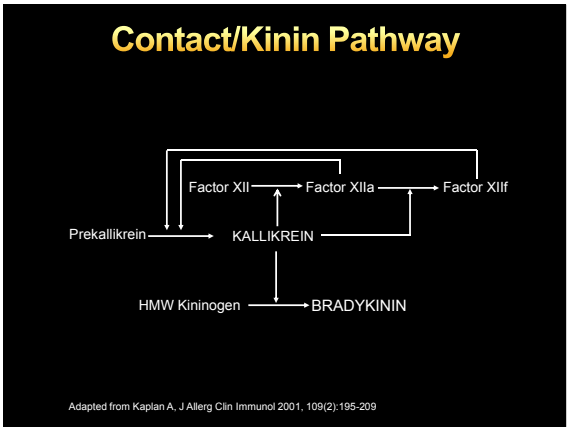
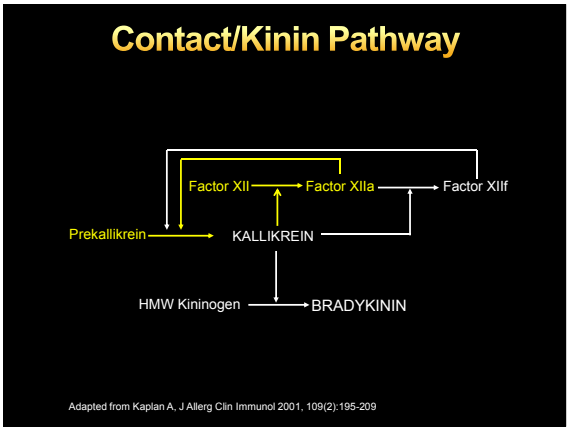
Acquired C1-INH I/II	Low	Low	<30%	Normal/ Low	Low
ACE inhibitor	**Normal**	**Normal**	**Normal**	**Normal**	**Normal**
Idiopathic angioedema	**Normal**	**Normal**	**Normal**	**Normal**	**Normal**


Diagnostic Algorithm for Angioedema
Normal
Low
Normal
Low
Low
Normal
Normal
Low
slide courtesy of Dr. Bruce Zuraw
AAE=Acquired AngioEdema


Contact/Kinin Pathway
Factor XII
Factor XIIa
Factor XIIf
Prekallikrein
KALLIKREIN
HMW Kininogen
BRADYKININ
Adapted from Kaplan A, J Allerg Clin Immunol 2001, 109(2):195-209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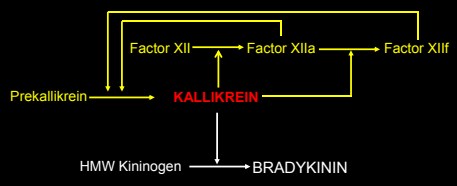

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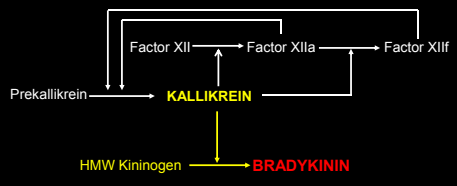

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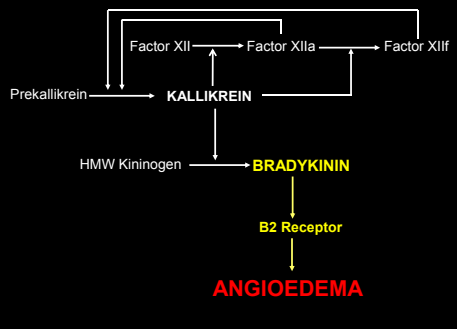
Bradykinin-Induced Angioedema

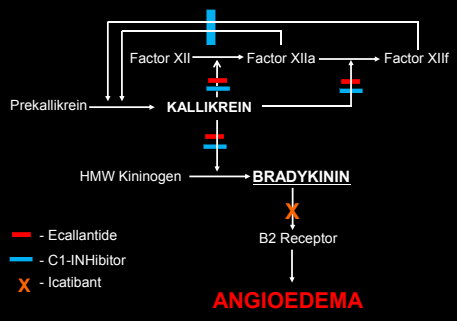


Hereditary Angioedema
Available Treatments

- Acute attacks
  - Supportive care: airway support, analgesics, fluids, time
  - Human plasma-derived C1-INH, ecallantide, icatibant
  - Fresh-frozen plasma
- Short-term or pre-procedural prophylaxis
  - Human plasma-derived C1-INH
  - High dose androgens (danazol, stanozolol)
  - Fresh-frozen plasma
- Long-term prophylaxis
  - Androgens
  - Anti-fibrinolytics (epsilon aminocaproic acid, tranexamic acid)
  - Human plasma-derived C1-INH

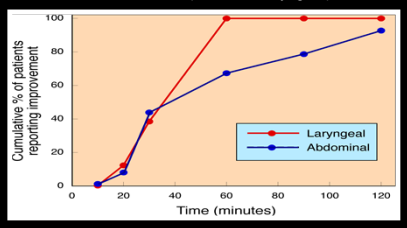
Tourangeau LM, Zuraw BJ: *Curr Allergy Asthma Rep.* 2011;11(5):345-351.

New Therapies for HAE



Angioedema Plasma C1-INH Replacement Therapy

- Multiple studies demonstrating efficacy
  - Efficacy first demonstrated >25 years ago
  - Response rate of virtually 100%
    - 629 / 630 attacks (193 / 193 laryngeal)

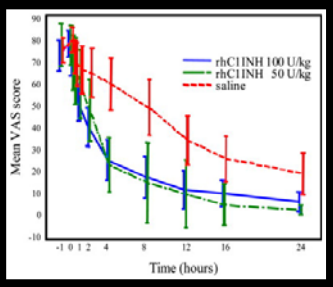


Bork K, Barnstedt SE. *Arch Intern Med.* 2001;161:714-718.
Bork K, et al. *Transfusion.* 2005;45:1774-1784.

slide courtesy of Dr. Bruce Zuraw

Recombinant C1-INNH

Time to beginning of relief



Zuraw B, Cicardi M, Levy RJ et al. *J Allergy Clin Immuol* 2010 Oct;126(4):821-827.e14

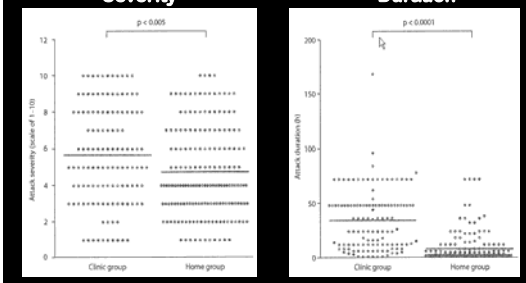
Home Administration of C1-INH for HAE

- Offers possibility of earlier Rx and better sx control
- Recommendations:
  - Inclusions / exclusions; training programs
  - Prophylaxis, route of administration
  - Counseling / consent
- Demonstrated ability of self / partner to infuse allows:
  - Increased QoL, flexibility & convenience
  - Decreased time to treatment, severity / duration of attacks
- Patient selection and training required to achieve reasonable and effective results

Longhurst H, et al. *Allergy Asthma Clin Immunol*. 2010:6(1):22.
Levi M, et al. *J Allergy Clin Immunol*. 2007;117:904-908.
Dagen C, et al. *Allergy Asthma Clin Immunol*. 2010;6(1):11.
Bygum A, et al. *Eur J Dermatol*. 2009;19(2):147-151.
Kreuz W, et al. *Transfusion*. 2009; 49(9);1987-1995.

Severity and Duration of HAE Attacks in the Clinic and at Home

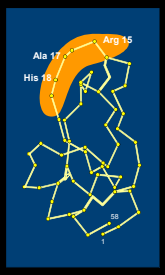
Severity **Duration**



Tourangeau L et al., *Int Arch Allergy Immunol* 2012;157:417-424.

HAE Plasma Kallikrein Inhibitor (Ecallantide)

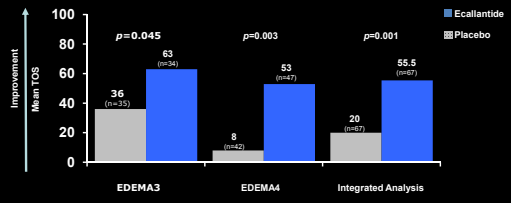
- Potent human plasma kallikrein inhibitor
- 60–amino acid protein produced in *Pichia pastoris*
- Subcutaneous administration
- Half-life ~2 hrs
- Two phase III double-blind, placebo-controlled studies:
  - Cutaneous, abdominal, facial attacks
  - Both studies showed efficacy (N=168)
  - Approved all attacks age 16 and older
  - Second dose at 4 hours if needed



Cicardi M, et al. *N Engl J Med*. 2010;363(6):523-531

Ecallantide

Improvement of Acute Attack Symptoms at 4 Hours



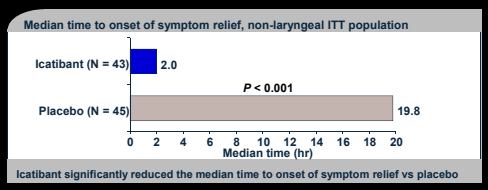
**** Treatment Outcome Score (TOS) is a measure of symptom response to treatment. A TOS value >0 reflected an improvement in symptoms from baseline.***

Cicardi M, et al. *N Engl J Med*. 2010;363(6):523-531.
Levy RJ,et al.*Ann Allergy Asthma Immunol*. 2010;104(6):523-529.

Icatibant

Second-generation bradykinin B2-receptor antagonist

- Subcutaneous administration with half-life of ~1.2 hours
- Approved for all types of attacks age 18 and older
- Dose maybe repeated at 6 hours. No more than 3 doses in 24 hours
- Primary adverse event injection site reaction (97%)
- Approved for self administration



Cicardi, et al. NEJM 2010; 363(6):532-541

Lumry, et al. Ann Allergy Asthma Immunol. 2011. 107(6): 529-537.

Comparison of Emerging HAE Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Plasma-derived C1-INH	• Infectious risk • Potential infusion reactions	• Needs IV access • Limited supply	• Extensive clinical experience • Corrects the fundamental defect • Relatively long half-life • Both pdC1INH products FDA-approved for self-administration	• Berinert: FDA approved for acute attacks in 2009 • Cinryze: FDA approved for prophylaxis 2008; additional study requested for acute attacks
Recombinant C1-INH	• Potential allergic reactions • Antibody formation to protein	• Needs IV access • Short half-life	• Corrects the fundamental defect • No human virus risk • Scalable supply	• Rhucin/Ruconest: approved in Europe; additional US study ongoing
Ecallantide	• Allergic reactions • Antibody formation to protein • Local injection reactions	• Short half-life • Requires health care provider administration due to anaphylaxis risk	• No infectious risk • More potent than C1-INH at site of action • Subcutaneous administration	• Kalbitor: FDA approved for acute therapy in December 2009
Icatibant	• Local injection reactions	• Short half-life	• No infectious risk • Stable at room temperature • Subcutaneous administration • FDA-approved for self-administration	• Firazyr: FDA approved for acute therapy in August 2011

Individualization of HAE Therapy

Patient factors

- Age
- Sex
- Type / pattern of attacks
- Access to medical care
- Geographic location
- Other medical problems
- Patient preference
- Quality of life

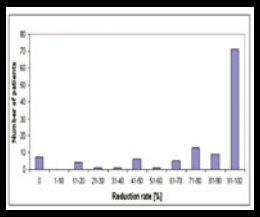
Medication factors

- Efficacy and safety
- Route of administration
- Site of care
- Treatment complications
- Availability
- Cost

Long–Term Prophylaxis of HAE

- Does the patient need long-term prophylaxis?
  - Not all HAE patients
  - Need varies by individual
    - Frequency, severity, and type of attacks
    - Availability of care
    - Failure of on-demand therapy
- Modalities
  - Anabolic androgens (attenuated or impeded)
    - Increase C1-INH levels
  - Antifibrinolytics
    - Mechanism of action uncertain
  - C1-INH replacement
- Acute treatment should be available for ALL patients on prophylaxis

Efficacy of Androgens for Long-Term Prophylaxis in HAE



58 of 118 subjects discontinued androgens: 41 due to adverse effects, 7 due to ineffectiveness

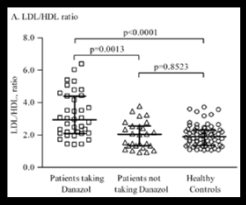
Bork K, et al. *Ann Allergy Asthma Immunol.* 2008;100:153-161, with permission.

Contraindications to Androgens

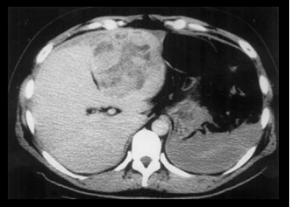
- Pregnancy
- Lactating women
- Hepatic disease (HCV hepatitis, etc)
- Children (before Tanner stage V)
- CA (prostate / breast)
- Nephrotic syndrome

Side Effects of Anabolic Androgens

Can include virilization, hepatotoxicity, headache, hypertension, weight gain, menstrual abnormalities, acne, psychological effects, and altered libido



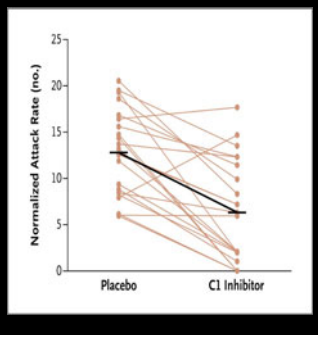
Széplaki G, et al. *J Allergy Clin Immunol.* 2005;115:864-869; with permission.



Bork K, Schneiders V. *J Hepatol.* 2002;36:707-709; with permission.

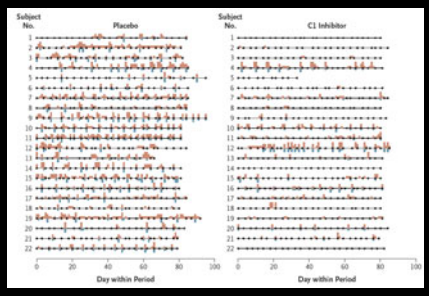
C1-INH-nf Prophylaxis Associated with Lower HAE Attack Rates

- Average normalized attack rate
  - 12.73 *vs* 6.26, placebo *vs* C1-INH-nf
- Average difference in attack rates
  - 6.47 (P<0.001)



Zuraw B, et al. *N Engl J Med.* 2010;363:513-522, with permission.

C1-IHN-nf Prophylaxis Associated with Lower HAE Attack Rates



Zuraw B, et al. *N Engl J Med*. 2010;363:513-522, with permission.

Considerations for Long Term Prophylaxis

- Failures of "on demand therapy"
- Patients who suffer from consequences of HAE and have decreased quality of life such as:
  - > 1 attack / mo
  - Limited access to healthcare OR rapid onset of attacks
  - Prior intubation or ICU stay
  - Prior upper airway edema
  - Significant anxiety
  - > 10 days lost from school or work / year
  - Significantly decreased QoL
  - Narcotic dependence
- Acute treatment should be available for ALL patients on prophylaxis

Dagen C, et al. *Allergy Asthma Clin Immunol*. 2010;6(1):11.

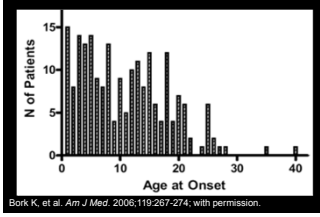
Short-Term Prophylaxis

- Indications
  - Extensive dental work
  - Surgical procedures
  - Other invasive procedures
- Modalities
  - C1-INH concentrate
    - 500–1500 units 1–6 hours before procedure
  - Fresh-frozen plasma
    - Two units 1–12 hours before procedure
  - High-dose androgens
    - Requires at least 1 week of treatment

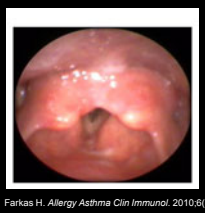
Adapted from Zuraw BL. *N Engl J Med*. 2008;359:1027-1036.

Pediatric Care of HAE

- Onset of symptoms occurs during childhood in majority of cases
- Anatomical characteristics require special considerations when establishing diagnosis and management
- 1 mm edema reduces airway diameter
  - 27% in adults, 44% in children, 75% in neonates



Bork K, et al. *Am J Med*. 2006;119:267-274; with permission.



Farkas H. *Allergy Asthma Clin Immunol*. 2010;6(1):19.

Case 3 - Aaron

Aaron is an 18 year old male who presents to the office with recurrent abdominal pain since age 13

- He was healthy until adolescence when he began to develop sporadic abdominal pain which initially occurred a couple of times a year
- Over the last 2 years, he has experienced more frequent and severe abdominal pain
- No response to proton pump inhibitors and anti-motility agents
- He had an appendectomy and another "exploratory" abdominal surgery in the past six months

Case courtesy of Marc Riedl

Case 3 - Aaron

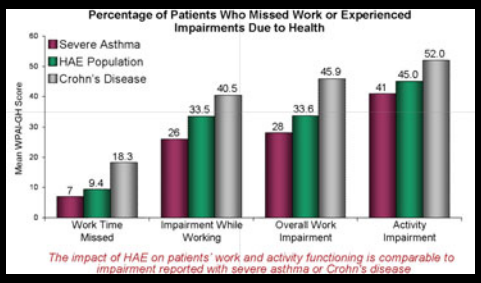
- Extensive evaluation by 3 physicians unrevealing and a diagnosis of irritable bowel syndrome given
- He has experienced occasional swelling of his hands and feet not associated with rash or urticaria
- His father and uncle have similar episodes of swelling of hands and feet attributed to food allergy
- He has dropped out of high-school basketball due to frequent pain and is currently missing about 10 days of school a month

Burden of Illness of HAE

- Web-based survey of HAE pts:
- Attack characterization, treatment, side effects, pain, functional & emotional burden of HAE
- Patients reported significantly worsened health, 42.5% depression and 34% work impairment
- Considerable burden across physical and mental domains impacting education, career and work production
- Substantial economic burden

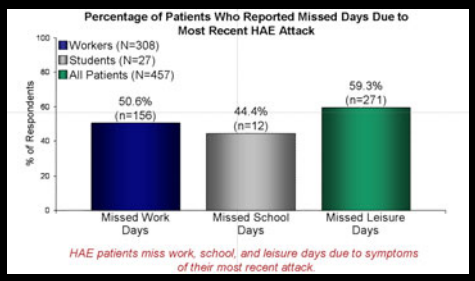
Lumry W, et al. *Allergy Asthma Proc.* 2010;31:407-414.
Wilson D, et al. *Ann Allergy Asthma Immunol.* 2010;104:314-320.

Hereditary Angioedema
Burden of Illness: Impairment



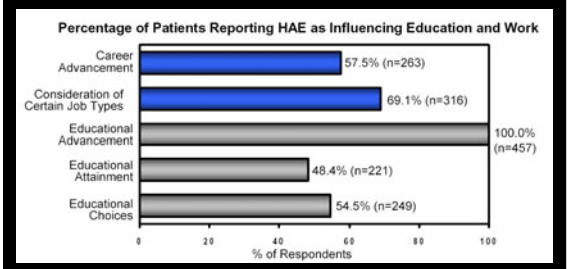
Lumry WR, Castaldo AJ et al. *Allergy Asthma Proc.* 2010 Sep;31(5):407-14.

Hereditary Angioedema
Burden of Illness: Days Lost



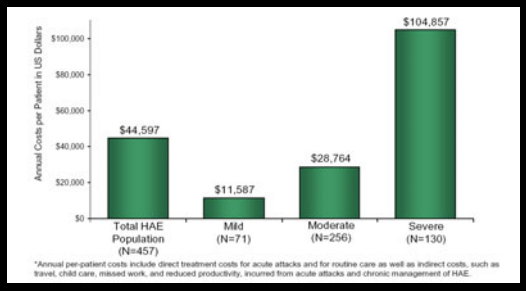
Lumry WR, Castaldo AJ et al. *Allergy Asthma Proc.* 2010 Sep;31(5):407-14.

Hereditary Angioedema
Burden of Illness: Education



Lumry WR, Castaldo AJ et al. *Allergy Asthma Proc.* 2010 Sep;31(5):407-14.

Hereditary Angioedema
Burden of Illness: Annual Costs



Wilson DA, Bork K et al. *Ann Allergy Asthma Immunol.* 2010 Apr;104(4):314-2

HAE International HAE Consensus Conference

- All HAE patients should have on-demand therapy
  - Patients should be trained for self-administration
  - Attacks at all locations are eligible for treatment
  - Attacks should be treated as soon as they are recognized
  - Hospitalize for progressing laryngeal involvement
- Long-term prophylaxis
  - Consider when optimized on-demand treatment fails
  - Androgens are contraindicated in patients who are:
    - ≤16 years of age
    - Pregnant / breastfeeding
    - Do not tolerate or accept androgens

Cicardi M, et al. Gargnano,Italy International HAE Consensus Conference. Allergy. 2012 Feb;67(2):147-57

Acquired C1 Inhibitor Deficiency

- Episodic attacks of angioedema without urticaria involving extremities, face, abdomen, larynx
- Onset usually at age 50 or older
- No family history of angioedema
- Laboratory features similar to hereditary angioedema (ie. low C4, low C1INH level and function but C1q low in 70% of cases)
- May be underlying treatable condition

Cicardi M, Zanichelli A. Allergy Asthma Clin Immunol. 2010, 28;6(1):1

Acquired C1 Inhibitor Deficiency Types

- **Type I**: Seen most commonly with B cell lymphoma or monoclonal gammopathy. Rare cases may occur with autoimmune disorders with B cell hyperreactivity
- **Type II**: Most commonly due to IgG antibody to C1 Inhibitor which prevents its ability to inactivate enzymes such as plasma kallikrein and factor XIIa. The monoclonal proteins are antibodies directed against C1 inhibitor
- There is an overlap in the two types, since most cases with lymphoma also have anti-C1 INH ab

Cicardi M, Zanichelli A. Allergy Asthma Clin Immunol. 2010, 28;6(1):1

Acquired C1 Inhibitor Deficiency Treatment

- Attenuated androgens, antifibrinolytics and/or immunosuppression therapy may be effective for prevention of attacks
- Plasmaphoresis may be effective
- For acute attacks, C1 inhibitor concentrate, where available, should be used, but may require very large doses secondary to high titer of anti-C1 INH
- Icatibant and ecallantide are expected to be effective
- Main treatment is treating the associated lymphoma or other underlying disease

Cicardi M, Zanichelli A. Allergy Asthma Clin Immunol. 2010, 28;6(1):1

Case 4 - Katherine

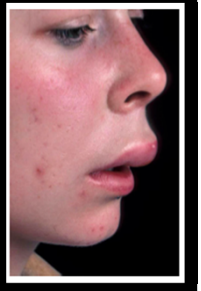
Katherine is a 32-year woman presenting to the office with recurrent facial and throat swelling for the past 2 years

- Her attacks occur about once a month
- Vary from mild lip swelling to severe laryngeal swelling with respiratory compromise
- She has been hospitalized 3 times with 2 ICU stays for severe angioedema
- No associated urticaria

Case courtesy of Marc Riedl

Case 4 - Katherine

- Mother and grandmother reported similar facial swelling though less severe
- Previous C4 testing normal during an asymptomatic period and her C1-INH tests are "normal to borderline" according to patient
- Given antihistamines, corticosteroids, epinephrine in ED but required 48 hour ICU stays
- Currently on cetirizine 40mg qd, hydroxizine 100mg qhs, prednisone 40mg daily for 6 weeks with 1 mild-moderate and 2 severe facial swelling episodes during that time
- Frightened she will asphyxiate



Bork, *Immunol Allergy Clin NA.* 2006;26:709-24

Complement Profile in Recurrent Angioedema

Type	C1-INH Level	C1-INH Function	C4 Level	C3 Level	C1q Level
HAE type I	<30%	<30%	Low	Normal	Normal
HAE type II	Normal	<30%	Low	Normal	Normal
HAE with normal C1INH	Normal	Normal	Normal	Normal	Normal
Acquired C1-INH I/II	Low	Low	<30%	Normal/ Low	Low
ACE inhibitor	Normal	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal	Normal

Hereditary Angioedema with Normal C1INH

- First described in 2000 independently by Bork in Germany and Binkley in Canada [1,2]
- HAE with normal C1INH has been referred to by multiple names including: New HAE, Estrogen-dependent HAE, and Type III HAE
- HAE with normal C1INH preferred
- Two subtypes are defined:
  - HAE with normal C1INH and fXII mutation
  - HAE with normal C1INH of unknown cause

1. Bork K et al. Lancet. 2000;356(9225):213-7.
2. Binkley KE, Davis A. J Allergy Clin Immunol. 2000;106(3):546-50.

HAE With and Without Normal C1INH

Finding	HAE due to C1INH deficiency	HAE with normal C1INH
Average age of symptom onset	11.7 ± 7.7 years	26.8 ±14.9 years
Gender	Female = Male	Female >> Male
Attack location	HAE with normal C1INH	f XII mutation
Abdominal	Almost all patients experience	50% of patients
Facial	Occasional	Common
Tongue	Not common	Common
Erythema marginatum	Common	Not seen
Multi-organ attacks	Common	Uncommon
Disease free intervals	Generally short	May be considerable
Penetrance	Generally high rare asymptomatic carrier	Generally low; may see obligate asymptomatic carrier

Zuraw BL et al. 2012 in press

Hereditary Angioedema with Normal C1INH

- Autosomal dominant inheritance
- 10-20% as prevalent as HAE with C1INH deficiency
  - 1:250,000 to 1:500,000 individuals
- Highly variable penetrance but may be low with asymptomatic carrier state particularly in men
- Females much more commonly affected and have more severe disease
- Increased estrogen state (pregnancy, HRT, OCP) often required for attacks to occur
- Factor XII Mutations occur in the minority of patients

Zuraw BL et al. 2012 in press

Hereditary Angioedema with Normal C1INH - Estrogen Impact

First Author	Number of Families	Number of Patients	Estrogens Required for Symptoms	Worsens Symptoms	No impact on Symptoms	Unknown
Binkley	1	7	7	0	0	0
Martin	1	4	3	1	0	0
Bork	13	35	20	10	5	0
Vitrat-Hincky	15	22	5	12	4	1
Bouillet	1	2	0	2	0	0
Picone	2	6	6	0	0	0
Martin	1	2	0	2	0	0
Serrano	5	10	10	0	0	0
Prieto	1	4	4	0	0	0
Baeza	1	3	3	0	0	0
Total	**41**	**95**	**58**	**27**	**9**	**1**

Zuraw BL et al. 2012 in press

Factor XII Mutations in HAE with Normal C1INH

First Author	Number of Families	No Mutation Found	Thr309Lys	Thr309Arg	Other Mutation
Dewald	20	14	5	1	0
Binkley	1	0	1	0	0
Bouillet	1	0	1	0	0
Baeza	1	0	0	0	1
Nagy	1	0	1	0	0
Prieto	1	0	1	0	0
Cichon	1	0	1	0	0
Vitrat-Hincky	15	12	3*	0	0
Picone	2	0	2	0	0
Martin	1	0	1	0	0
Bork	53	40	11	2	0
Bork	1	0	0	0	1

Zuraw BL et al. 2012 in press

* fXII Thr309Lys versus Thr309Arg mutation not specified

Hereditary Angioedema with Normal C1INH: Diagnosis

- Diagnostic criteria
  - History of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema; and
  - Documented normal C4, C1 inhibitor antigen, and C1 inhibitor function, and
  - One of the following:
    - Demonstration of a factor XII mutation that is associated with the disease
    - A positive family history of angioedema and documented evidence of lack of efficacy of chronic high dose antihistamine therapy (Cetirizine 40mg/day for at least 1 month and an interval expected to be associated with 3 or more attacks

Zuraw BL et al. 2012 in press

Hereditary Angioedema with Normal C1INH: Treatment

- No randomized prospective clinical trials conducted
- Observations suggest disorder does not involve histamine or mast cell degranulation
- Drugs that are effective for HAE with C1INH deficiency appear to be helpful in HAE with normal C1INH specifically
  - 17 alpha-alkalated androgens, tranexamic acid
  - C1INH concentrate, ecallantide, icatibant
- Avoid estrogens (OCP, HRT), ACE-I and ARB's

Zuraw BL et al. 2012 in press

Angioedema - Conclusions

- Most often occurs in association with urticaria
- Common causes include allergy (food, drug, insect sting) and some physical triggers
- Treatment for allergic angioedema includes epinephrine, antihistamines and corticosteroids
- When angioedema occurs without urticaria, consider idiopathic, ACE inhibitor-induced, hereditary and acquired C1 inhibitor deficiencies
- Treatment with drugs affecting bradykinin production or action may be effective in non-histamine induced angioedema